REMARKS

This Reply is responsive to the Office Action dated October 11, 2001. Entry of the foregoing and reconsideration on the merits pursuant to 37 CFR 1.112 is respectfully requested.

The application has been amended as set forth above. In accordance for the new rules for amending applications set forth in 37 CFR 1.121, which took effect on March 1, 2001, a marked up version of the claims showing all amendments is attached hereto as an appendix.

First, the specification has been amended to replace references to URLs. For instance, the reference to http://telomeres,virtualave.net/regulation.html on page 6 of the specification was deleted and the following reference cite was included: Dionne and Wellinger (1996) Proc. Natl. Acad. Sci. USA 93: 13902-13907. As shown by the attached copy of the referenced URL and the corresponding list of references from the same website, the subject matter cited in the specification was initially disclosed in the Dionne reference. Therefore, no new matter is incorporated by citing the reference cited by the website rather than the website itself.

In addition in this same paragraph, cites were added for Holt, Belair and Weng, and reference to the website that in turn cites these references was deleted.

Similarly, the reference to http://abcnews.go.com/sections/science/Daily News/ clones980522.html (1998) on page 8 of the specification was amended to read ABC News (Reuters), Daily News, May 22, 1998.

Likewise, the reference to claim.springer.de/EncRef/CancerResearch/samples

/0001.htm on page 26 of the specification was replaced by reference to the attached abstract, Horikawa et al., 1998, Repression of telomerase catalytic subunit by a gene on human chromosome 3 that induces cellular senescence, Mol. Carcinog. 22(2): 65-72. As shown by the attached copy of the referenced URL, no cite was provided for the information gleaned from this cite, e.g., that there was evidence existing that a gene on chromosome three was involved in the transcriptional regulation of hTERT. However, a search of the PubMed database turned up the Horikawa reference which reports the same information, and which was available in the art at the time the subject application was filed. Therefore, addition of the reference to the Horikawa reference would not constitute new matter since it was known in the art at the time the application was filed, and it substitutes for a URL that discloses the same information.

Claim 1 was amended to limit the claimed method to the use of mammalian cells, and to define a rejuvenated cell as one that has telomeres that are on average at least as long as those of cells from a same age control teratoma that is not generated by nuclear transfer techniques. Support for the use of mammalian cells may be found on page 19, line 3 of the specification. The definition for a rejuvenated cell may be found at page 15, lines 18-20. This definition was included in original claim 3, which was canceled above now that the limitation recited therein was incorporated into amended claim 1.

Claim 4 was amended to depend on claim 1 rather than on itself.

Claim 7 was amended to define "alteration to the genome" by incorporating the alternative definitions provided in original claims 17 and 18, and to clarify that it is the "first" primary cell referred to in the method of claim 1 that has the genetic alteration (however, the rejuvenated cell, by the nature of the cloning process, would also have the genetic alteration).

Claims 17 and 18 were canceled because the limitations recited therein were incorporated into claim 7.

Claim 8 was amended to limit the claimed method to the use of mammalian cells, and to delete reference to a second teratoma for clarity purposes.

Claim 13 was amended to delete the parenthetical for clarity purposes.

Claims 21 and 22 were amended to limit the claimed methods to the use of mammalian cells, and to clarify that the claimed method comprises generating a rejuvenated primary cell, rather than rejuvenating a particular cell *per se*, as pointed out in lines 1-2 of page 8 of the official action.

Claim 25 was amended to limit the claimed method to the use of mammalian cells, and to clarify that the mammal formed by the claimed method has the same genotype as the genetically altered cell of Claim 24. In addition, claim 25 was amended to indicate that the embryo formed in the method is implanted into a recipient female of the same species for full term development. Claim 25 was also amended to delete reference to an embryonic stem cell since embryonic stem cells cannot develop into an animal in utero because they are past the point in development where the trophectoderm forms.

Claim 29 was amended to limit the claimed method to the use of mammalian cells.

Claim 37 was amended to clarify that the cell donating the genetic material is a "primary" cell; i.e., a cell that is not tumorigenic or transformed, and is capable of being reprogrammed and of facilitating embryonic development after nuclear transfer, as described on page 15, lines 14-18, of the specification. Claim 37 was also amended to indicate that the method comprises transferring either the primary cell, or the chromosomes of said cell, into a

recipient oocyte, support for which is found in the specification, for example, on page 17, lines 17-19.

Claim 39 was amended to more clearly identify the "nucleated" oocyte from which the embryo or ES cell is generated, and to accord with the language of amended claim 37.

No new matter was added by way of any of the above amendments.

Turning now to the Office Action, the declaration is apparently defective because the correction to Jose Cibelli's citizenship was not signed and dated. **A substitute declaration has been prepared and given to the inventors; however, since one of the inventors has not yet been able to execute it, the signed and dated declaration will be submitted in a supplemental response as soon as possible.**

The specification was objected to for incorporating by reference several URLs. The specification was amended above to delete reference to URLs and include an alternative reference where appropriate. The objection is therefore moot.

Claims 1-39 were rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabled for a method of providing primary cells comprising: a) enucleating an oocyte of a first mammalian species and transferring the nucleus of the primary cell into the oocyte; b) activating the nt unit; c) culturing the activated nt unit in an immunocompromised mouse to produce a teratoma; and d) isolating a differentiated cell from said teratoma, allegedly fails to enable the use of any source of host cell nor the use of any organism besides a mammalian species. Without necessarily agreeing with the rejection, applicants note that the claims were amended above and are now limited to the use of mammalian cells. Therefore, this ground for the rejection is moot.

In addition, with reference to claims 25-39, the Office Action indicates that the specification does not enable the implantation and propagation of an nt unit in a pseudopregnant female that is of different species that the donor cell. Without necessarily agreeing with the rejection, applicants note that claim 25 was amended above to limit the implantation step to the use of a same species surrogate female. However, none of the other rejected claims appeared to require such a limitation.

For instance, claim 29 involves the use of a cloned mammalian inner cell mass, blastocyst, teratoma, embryo, fetus or animal, and as is appropriate, the claim does not specify that any of these are produced using a surrogate female. One of ordinary skill in the art would know upon reading the present disclosure, in view of the state of the art, how to isolate each of these cloned entities. For example, the skilled artisan would realize that one need not implant a nuclear transfer unit into a surrogate female of any species to obtain an inner cell mass, blastocyst, teratoma or embryo. Further, the skilled artisan would know that isolation of a fetus or animal would require propagation in a surrogate mother of the same species. It is not necessary to spell out something that the skilled artisan would recognize as evident. Nor would it be appropriate to include reference to a surrogate female when all the embodiments encompassed by the claimed method do not require the use of a surrogate female. Reconsideration and withdrawal of this ground for the rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

Claims 1-39 were rejected under 35 U.S.C. §112, second paragraph for alleged indefiniteness. Specifically, claim 1 is said to be unclear in the recitation of "rejuvenating a primary cell," because the method results in the production of a different and unique cell. Applicants can see the Examiner's point, and have amended claim 1 to read "isolating a rejuvenated primary cell" rather than "rejuvenating a primary cell." Further, the claim was

amended to include a definition of the word "rejuvenated" as it is defined in the specification. Therefore, this ground for the rejection is moot. Although not objected to, claims 21 and 22 were similarly amended to replace references to rejuvenating a primary cell with recitation of generating a rejuvenated primary cell.

Claim 3 was rejected for antecedent basis issues. However, since claim 3 is now canceled, this rejection is moot.

Claim 4 was rejected because it depended on itself. Claim 4 was amended above to depend on claim 1. Therefore, this rejection is moot.

Claim 7 was rejected because the nature of the recited genetic alteration is unclear, and because it is allegedly unclear when the modification is introduced, i.e., at the stage of the original primary cell or the rejuvenated primary cell. Claim 7 was amended above to include the definition of a genetic alteration, and to clarify that the genetic alteration is present at the stage of the original primary cell. Thus, the rejection should now be withdrawn.

Claim 8 was rejected because it was allegedly unclear if the second teratoma is generated by the primary cell, the recipient oocyte or the ICM. Claim 8 was amended to delete reference to a second teratoma since it is sufficient to say that the new cell has telomeres that are at least as long as a same-age control cell not generated by nuclear transfer. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 13 was rejected because it was allegedly unclear as to whether the parenthetical contained an intended use or a limitation. Claim 13 was amended to delete the parenthetical, because the method entails the making of a tissue whether or not its purpose be for transplantation.

Claim 25 was rejected because it was unclear how an animal having the "same genotype" can also be genetically altered. Claim 25 was amended to clarify that the animal is cloned from a primary cell that is genetically altered, and therefore the animal has the same genotype as the genetically altered cell.

The rejections raised under 35 U.S.C. §112, second paragraph, have been addressed by the amendments and remarks above. Therefore, withdrawal of the rejections is respectfully requested.

Claims 1-39 were rejected under 35 U.S.C. §102(a/e) as being allegedly anticipated by Strelchenko (US 6,011,197) or Damiani (US 6,258,988) as further evidenced by Evans et al. At the outset, applicants note that Damiani was not provided in the mailing sent to applicants, and a seacrh for the cited patent number on the U.S. PTO's website revealed that the cited patent number was incorrect. Applicants assume that what was intended was Damiani US 6,258,998, and applicants' response has been prepared with this understanding.

Also, one publication in particular and several patents were included with the Office Action mailing and were cited on the PTO-892 form but were not cited in the Office Action. Specifically, the PTO-892 form cites US patents 6,235,969; 6,235,970; 6,194,202; and a publication by Howell-Skalla et al. A telephone call to the Examiner confirmed that there was no reason for these patents to have been cited on the PTO-892 form, and indeed there was no intention to cite them in the Office Action. Therefore, applicants have disregarded these references.

Returning to the §102 rejection based on Strelchenko or Damiani as evidenced by Evans, the rejection was made because it is unclear how the claimed methods and resulting cells are materially different from the methods of nuclear transfer known in the art. Thus,

Strelchenko was cited for teaching nuclear transfer to clone a bovine, and Damiani was cited for teaching nuclear transfer to clone an ovine. Evans was cited as supporting the rejection because although Strelchenko and Damiani do not discuss transferring heterologous genetic material from the mitochondria, at the time of the claimed invention it was allegedly known as evidenced by Evans that transfer of mitochondria occurs during nuclear transfer. Applicants respectfully traverse the rejection.

First, it is not clear to applicants why Evans was cited to support the rejection, because it is irrelevant whether or not mitochondria are transferred along with the nucleus during nuclear transfer. The methods of the present invention comprise transferring a mammalian primary cell, or the nuclei or chromosomes of said cell, into a mammalian oocyte and generating a teratoma, the cells of which have telomeres at least as long as same age control cells that were not generated by nuclear transfer. The present invention also comprises transferring a senescent or near-senescent mammalian cell, or the nuclei or chromosomes of said cell, into a mammalian oocyte, and generating an embryo, fetus, or animal, the cells of which have telomeres at least as long as same age control cells. The present invention has nothing to do with the mitochondrial DNA content. Therefore, it is not clear why Evans is added in support of the rejection.

Furthermore, even though Evans was cited as teaching that mitochondrial DNA may be transferred during nuclear transfer, Evans also teaches that the only mitochondrial DNA nevertheless detected in a nuclear transfer derived animal is that from the recipient oocyte (see the abstract). Thus, if anything, Evans stands for the premise that cells and animals generated by nuclear transfer are different entities than the donor cells used to make them, in that they have a different mitochondrial genome. But again, this is a fact that is not at issue.

The Office Action states on page 7, first paragraph, that the present invention relies "in great part" on applicants' observation that a donor cell nucleus can be reprogrammed to become a pluripotent cell when transferred to an oocyte and properly cultured. If this was the extent of applicants' teaching, then Strelchenko would for instance be anticipatory, in that it teaches "re-programming" non-totipotent cells into totipotent cells (col. 2, line 54, for instance). But the present invention involves more than mere "reprogramming" of a non-totipotent cell into a totipotent one, in that the present invention also generates "rejuvenated" cloned cells that have telomeres that are just as long as a similar non-cloned cell.

As discussed in the specification in the background section, there have been recent concerns regarding the genetic age of cloned cells as reflected in the lengths of their telomeres. A recent report by Shiels et al. (Nature (1999) 399: 316), involving Dolly, the cloned sheep, suggests that nuclear transfer did not restore telomeric length, and that the telomeres at the ends of Dolly's chromosomes are just as short as those in the donor cell used to clone her. The implications of these findings are particularly relevant for the cloning of replacement cells and tissues for human transplantation, because it could mean that transplanted organs may undergo premature senescence and could actually aggravate the disease which the replacement cells are intended to treat. The Shiels et al. report also raises questions as to whether cells created by nuclear transfer will undergo premature senescence and whether cloned animals generated by nuclear transfer will exhibit decreased life spans. This in turn has serious implications for the cloning and re-cloning of high quality farm animals, which, prior to the report, was considered to be advantageous over traditional breeding techniques which are dependent on the animals reaching mating age before another generation may be propagated.

Not only does the observation regarding the shortened telomeres of cloned cells have serious implications for the field of organ transplantation, but it also calls into question the extent of genetic manipulations that may be performed to somatic cells which are to be used for nuclear transfer. For instance, a major advantage of nuclear transfer technology is that somatic cells may be more readily maintained in culture and transfected with transgenes than embryonic stem cells. This property facilitates the production of animals that produce therapeutic proteins, for instance cows which express transgenes from mammary-specific promoters enabling the production of therapeutic proteins in milk. If successive cell division decreases telomere length and the subsequent stability of clones generated therefrom such that cells may not be maintained in culture so as to facilitate necessary genetic alterations, then the utility of cloning technology would be significantly compromised. For instance, if cells used for nuclear transfer are not permitted to undergo a series of genetic manipulations, i.e., either consecutively in culture or consecutively through successive cloning, it will be virtually impossible to generate animals, cells and tissues with multiple genetic manipulations. The ability to perform such complex genetic manipulations may be necessary, for example, to correct genetic abnormalities in donor cells from patients having deleterious mutations before such cells are used for nuclear transfer and organ transplantation.

Thus, prior to the present invention, known nuclear transfer techniques resulted in cloned cells, embryos, animals, etc. having telomeres that are the same length as the donor cell used to create them. Therefore, such cloned cells have telomeres that are the same length as cells which are significantly older. The present invention, in contrast, results in a rejuvenation of telomere length via nuclear transfer, and thus results in cloned cells, embryos, animals, etc. that have telomeres that are just as long as a non-cloned cell of the same age, i.e., a cell not created by nuclear transfer.

The present invention is based on the unprecedented discovery that telomerase is activated upon nuclear transfer when a senescent or near-senescent cell is used as a nuclear donor. Thus, the methods of the invention may be used to increase the lifespan of a primary cell, e.g. a cell which is nearing senescence, either by reaching the natural limit on population doublings or as a result of harsh selection conditions for complex genetic alterations. Such a method is actually counterintuitive to what one of skill in the art would have believed when faced with the knowledge that nuclear transfer does not regenerate telomeres, in that the first instinct would be to use a donor cell that is as young as possible (thereby precluding significant in vitro culture and making compound genetic manipulations difficult). Instead, applicants have found that it is the use of a donor cell nearing the end of its natural doubling life that results in the activation of telomerase, the rejuvenation of telomeres, and the resetting of the cell's lifespan.

Neither Strelchenko nor Damiani teach that a cell's genetic lifespan, i.e., the telomeres of a cell's chromosomes, may be regenerated using nuclear transfer. In fact, the methods disclosed in Strelchenko employ the same type of donor cell used to create Dolly, i.e., a quiescent cell (see the paragraph bridging columns 11 and 12). Quiescent cells are cells that have been serum-starved, and are different than cells that have naturally aged such that they are at the end of their population doublings (senescent cells). Furthermore, the use of quiescent cells as nuclear donors results in cloned cells that do not have regenerated telomeres (as evidenced by Dolly). Therefore, the methods of the prior art do not teach methods of nuclear transfer that result in rejuvenated primary cells, i.e., cells that have telomeres that are just as long as non-cloned cells.

Furthermore, neither Strelchenko nor Damiani disclose or suggest transferring a mammalian primary cell, or the nuclei or chromosomes of said cell, into a mammalian oocyte and generating a teratoma, nor do they disclose or suggest transferring a senescent or near-

senescent mammalian cell, or the nuclei or chromosomes of such a cell, into a mammalian oocyte, and generating an embryo, fetus, or animal.

In view of these remarks, reconsideration and withdrawal of the rejection under §102 (a/e) is respectfully requested.

Claims 1-39 were rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Robl (WO 98/07841) as allegedly evidenced by Evans. Again, the basis for the rejection is that it is unclear how the claimed methods differ from those disclosed in Robl, and Evans is relied upon for teaching that mitochondria are exchanged during nuclear transfer. Applicants respectfully traverse the rejection.

Again, it is not clear to applicants why the teaching in Evans that mitochondria are transferred along with the nucleus in nuclear transfer is relevant to the present claims (see discussion of Evans above). It is also not clear to applicants why the teachings of Robl are relevant. The present claims are directed to isolating rejuvenated cells via nuclear transfer, where such cells have telomeres that are just as long as a same age cell that was not produced by nuclear transfer. There is no mention in Robl of telomere length or of rejuvenating the genetic lifespan of cells (see discussion above in response to §102(a/e) rejection). Rather, Robl concerns cross-species nuclear transfer of a donor cell into a recipient cell of a different species. The Robl reference does not disclose or suggest transferring a mammalian primary cell, or the nuclei or chromosomes of said cell, into a mammalian oocyte and generating a teratoma, nor does it disclose or suggest transferring a senescent or near-senescent mammalian cell, or the nuclei or chromosomes of such a cell, into a mammalian oocyte, and generating an embryo, fetus, or animal. In view of these remarks, reconsideration and withdrawal of the §102(b) rejection based on Robl is respectfully requested.

All issues raised by the Office Action dated October 11, 2001, have been addressed in this Reply. Accordingly, a Notice of Allowance is next in order. If the Examiner has any further questions or issues to raise regarding the subject application, it is respectfully requested that she contact the undersigned so that such issues may be addressed expeditiously.

Respectfully submitted,

Date: April 11, 2002

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APPENDIX

The following amendments were entered by way of the amended disclosure and claims presented for consideration above:

IN THE SPECIFICATION:

Please substitute the paragraph beginning at line 3 of page 6 with the following amended paragraph:

-- Some researchers have suggested that telomerase activity may be cell-cycle dependent. For instance, in 1996, Dionne reported the down-regulation of telomerase activity in telomerase-competent cells during quiescent periods (G phases) and hypothesized that telomerase activity may be cell-cycle dependent. See [http://telomeres,virtualave.net/regulation.html] Dionne and Wellinger (1996) Proc. Natl. Acad. Sci. USA 93: 13902-13907. Similarly, Kruk et al. reported a higher level of telomerase in the early S phase when compared to other points in the cell cycle (Biochem. Biophys. Res. Commun. (1997) 233: 717-722). However, other researchers have reported conflicting results, and have alternatively suggested that telomerase activity correlates with growth rate, not cell cycle (Holt et al. (1996) Mol. Cell. Biol. 16(6): 2932-2939; see also [Website, id., referencing] Holt et al. [, 1997] (1997) Proc. Natl. Acad. Sci. USA 94: 10687-92; and Belair et al. [, 1997] (1997) Proc. Natl. Acad. Sci. USA 9: 13677-13682). Still others have proposed that telomerase activation is mediated by other cellular activation signals, as evidenced by the upregulation of telomerase in B cells *in vitro* in response to CD40 antibody/antigen receptor binding and exposure to interleukin-4 ([Website, id., citing] Weng et al. [, 1997] (1997) Proc. Natl. Acad. Sci. USA 94: 10827-32; see also Hiyama et al. (1995) J. Immunol. 155 (8): 3711-

3715). But despite the rising interest in telomerase and its purported role in the process of aging and cellular transformation, the regulation of telomerase activity remains poorly understood. See, e.g., Smaglik, "Turning to Telomerase: As Antisense Strategies Emerge, Basic Questions Persist," *The Scientist*, January 18, 1999, 13(2): 8).--

Please substitute the paragraph beginning at page 8, line 6 with the following amended paragraph:

-- The present invention stems from the discovery that nuclear transfer techniques may be used to extend the life span of senescent or near-senescent cells by activating endogenous (cellular) telomerase activity. This provides particular advantages over recently publicized approaches for resolving the telomere loss seen in nuclear-transfer generated animals, which focus on the exogenous expression of a cloned telomerase gene to resolve telomere shortening in cloned mammals. For instance, researchers at Geron Corporation and the Roslin Institute have recently collaborated to combine Geron's cloned telomerase gene with nuclear transfer in order resolve telomere shortening in clones. See, e.g., [Businees] Business Wire, May 26, 1999. This announcement preceded the May 27th Nature report by researchers at Roslin Institute that two other sheep (after Dolly) cloned by nuclear transfer also exhibit shorter telomeres than age-matched controls. Researchers at the University of Massachusetts involved in cloning cattle also believed that transfecting donor cells with an exogenous telomerase gene might be beneficial for the lifespan of cloned animals, despite the observation that nuclear transfer seemed to rejuvenate senescent donor cells. [See http://abcnews.go.com/sections/science/Daily News/clones980522.html (1998)] ABC News (Reuters), Daily News, May 22, 1998.--

Please replace the paragraph beginning at page 26, line 13 with the following amended paragraph:

-- For instance, Xu et al. demonstrated that re-expression of the retinoblastoma protein in tumor cells induces senescence and inhibits telomerase activity (Oncogene (1997) 15: 2589-2596). A recent report also suggests that a gene on chromosome 3 may be involved in transcriptional repression of hTERT, the catalytic subunit of telomerase. See [http://claim.springer.de/EncRef/CancerResearch/samples/0001.htm] Horikawa et al. (1998) Mol. Carcinog. 22(2): 65-72. Several proteins have also been identified that interact directly with telomerase, such as p23/hsp90 (molecular chaperones) and TEP1 (telomerase associated protein 1). Id. Researchers at Lawrence Berkeley National Laboratory have purported cloned two additional human telomere-associated proteins (Tin 1 and Tin 2). Federal Technology Report, December 30, 1999, Partnership Digest, Technology Watch, p. 9. Thus, the regulatory mechanism identified by the present methods could operate by binding to or inhibiting the expression of a telomerase binding protein or a telomerase repressor, consequently increasing telomerase activity, but could also regulate telomerase activity by upregulating gene expression or enhancing protein stability.--

IN THE CLAIMS:

Kindly cancel claims 3, 17, and 18.

Kindly consider the following amended claims:

1. (Amended) A method of [rejuvenating] isolating a rejuvenated primary mammalian cell, comprising:

a. transferring a first primary mammalian cell, the nucleus from said first primary mammalian cell or chromosomes from a first primary mammalian cell to a recipient mammalian oocyte or egg in order to generate an embryo;

b. obtaining an inner cell mass, embryonic disc and/or stem cell using said embryo;

c. injecting said inner cell mass, embryonic disc and/or stem cell into an immune-compromised animal to form a teratoma;

d. isolating said resulting teratoma;

e. separating the different germ layers for the purpose of identifying specific cell types;

f. isolating a rejuvenated cell of the same type as the primary cell, wherein said rejuvenated cell has telomeres that are on average at least as long as those of cells from a same age control teratoma that is not generated by nuclear transfer techniques.

4. (Amended) The method of Claim [4] 1, wherein said telomeres are on average longer than those of cells from a same age control teratoma that is not generated by nuclear transfer techniques.

7. (Amended) The method of Claim 1, wherein said first primary cell has at least one alteration to the genome, wherein said genetic alteration comprises the transfection of at least one heterologous gene or the disruption of at least one native gene.

8. (Amended) A method of making a primary mammalian cell having the same genotype as a first mammalian cell which is of a different primary cell type, comprising:

a. transferring the nucleus from said first mammalian cell to a recipient mammalian oocyte in order to generate an embryo;

b. obtaining an inner cell mass, embryonic disc and/or stem cell using said embryo;

c. injecting said inner cell mass, embryonic disc and/or stem cell into an immune compromised [animal] mammal to form a teratoma;

d. isolating said resulting teratoma;

e. separating the different germ layers for the purpose of identifying specific cell types;

f. isolating a primary cell of a different type than the first primary cell,

wherein the telomeres of said new primary cell are at least as long the telomeres of a same age control cell [in a teratoma] not generated by nuclear transfer techniques.

13. (Amended) The method of Claim 11, wherein said primary cell is used to generate a tissue [(for transplantation into a patient in need of a transplant)].

21. (Amended) A method of performing compound genetic manipulations in [a] primary mammalian cells, comprising [rejuvenating said primary cell between genetic manipulations using nuclear transfer into a recipient oocyte, wherein said cell is passaged to a senescent or near-senescent state prior to nuclear transfer] transferring a senescent or near-senescent primary mammalian cell, the nucleus of said cell, or chromosomes from said cell, into a recipient mammalian oocyte and generating a rejuvenated primary cell between genetic manipulations of said primary cell.

22. (Amended) A method of performing compound genetic manipulations in [a] primary mammalian cells, comprising [rejuvenating said primary cell between genetic manipulations using nuclear transfer into a recipient oocyte, wherein said cell is induced into

a senescent or near-senescent state prior to nuclear transfer] transferring a senescent or near-senescent primary mammalian cell, the nucleus of said cell, or chromosomes from said cell, into a recipient mammalian oocyte and generating a rejuvenated primary cell between genetic manipulations of said primary cell.

25. (Amended) A method of making a [genetically altered animal] mammal having the same genotype as the genetically altered cell of Claim 24, comprising

a. transferring the nucleus of said cell into a recipient oocyte,

b. generating an embryo [or embryonic stem cell] from said nucleated oocyte,

c. introducing said embryo [or embryonic stem cell] into a recipient female of the same species, and

d. allowing said embryo or embryonic stem cell to fully develop such that said female delivers a newborn animal having the same genotype as said primary cell.

29. (Amended) A method of making a re-cloned mammalian inner cell mass, blastocyst, teratoma embryo, fetus or animal containing at least two genetic modifications, comprising:

a. obtaining a primary cell from [an animal] a mammal of interest,

b. making a first genetic modification to said primary mammalian cell by inserting heterologous DNA and/or deleting native DNA,

c. allowing said genetically modified primary mammalian cell to multiply to senescence or near-senescence,

d. using a first genetically modified mammalian senescent or near-senescent cell as a nuclear donor for nuclear transfer to an enucleated oocyte or an enucleated fertilized egg,

e. obtaining a cloned mammalian inner cell mass, blastocyst, teratoma, embryo, fetus or animal having said first genetic modification,

f. obtaining a cloned primary cell from said cloned mammalian inner cell mass, blastocyst, teratoma, embryo, fetus or animal,

g. making a second genetic modification to said cloned primary mammalian cell by inserting heterologous DNA and/or deleting native DNA,

h. allowing said second cloned primary mammalian cell to multiply until senescence or near senescence,

i. using a senescent or near-senescent cloned primary mammalian cell having said first and second genetic modifications as a nuclear donor for nuclear transfer to an enucleated oocyte or an enucleated fertilized egg, and

j. obtaining a re-cloned mammalian inner cell mass, blastocyst, teratoma, embryo, fetus or animal having said first and second genetic modifications.

37. (Amended) A method of re-setting the life-span of a senescent or near-senescent primary mammalian cell[s], comprising transferring said primary cell, the nucleus of said cell, or chromosomes from said cell, into a recipient oocyte.

39. (Amended) The method of Claim 37 further comprising generating an embryo or embryonic stem cell from said [nucleated] oocyte containing said cell, the nucleus of said cell, or chromosomes from said cell.